



CDEC FINAL RECOMMENDATION

ECULIZUMAB

(Soliris — Alexion Pharmaceuticals Inc.)

New Indication: Atypical Hemolytic Uremic Syndrome

Recommendation:

The Canadian Drug Expert Committee (CDEC) recommends that eculizumab not be listed.

Reasons for the Recommendation:

Two uncontrolled prospective studies had several important limitations, including a lack of clear diagnostic criteria for atypical hemolytic uremic syndrome (aHUS), the absence of a comparator group to examine outcome differences, short duration of follow-up, and lack of data regarding clinically important outcomes for patients with aHUS. Therefore, the clinical benefit of eculizumab could not be adequately established.

Background:

Eculizumab has a Health Canada indication for the treatment of patients with aHUS to reduce complement-mediated thrombotic microangiopathy (TMA). Eculizumab has been issued a marketing authorization without conditions for adults and adolescents aged 13 to 17 years, weighing more than 40 kg who have aHUS. In children less than 13 years of age and/or weighing less than 40 kg, eculizumab has been issued a marketing authorization with conditions (i.e., Notice of Compliance with Conditions), pending the results of studies to verify its clinical benefit.

Following an induction phase of 900 mg weekly for four weeks and 1,200 mg at week five, the recommended maintenance dosage is 1,200 mg every two weeks. Children weighing less than 40 kg are dosed according to weight. A supplemental eculizumab dose is administered when plasma therapy (PT) is required. Eculizumab is available as a 10 mg/mL solution for intravenous injection.

Submission History:

Eculizumab was previously reviewed by the Canadian Expert Drug Advisory Committee (CEDAC) for paroxysmal nocturnal hemoglobinuria to reduce hemolysis; it received a recommendation that it “not be listed at the submitted price” (see Notice of CEDAC Final Recommendation, February 19, 2010).

Summary of CDEC Considerations:

CDEC considered the following information prepared by the Common Drug Review (CDR): a systematic review of eculizumab trials, a critique of the manufacturer's pharmacoeconomic evaluation, and patient group-submitted information about outcomes and issues important to patients.

Patient Input Information

The following is a summary of information provided by one patient group that responded to the CDR call for patient input:

- Patients with aHUS report high amounts of emotional, financial, and responsibility-related stress leading to feelings of isolation, fear, hopelessness, anxiety, and depression.
- PT causes increased fatigue, confused thinking, and nausea post-treatment, and patients experience high total protein levels, increased blood pressure, and headaches. PT is only available in major hospitals; therefore, many patients must travel for treatment, which increases time and financial burdens on families. Parents of patients undergoing PT estimated that their children miss 30% to 40% of their school year, with the parent having 20% to 40% absenteeism from work.
- Patients indicated that treatment with eculizumab would not require the use of a central line and would allow them to avoid attending weekly or biweekly plasma infusions, which can last upwards of seven hours.

Clinical Trials

There were no randomized controlled trials (RCTs) identified in the CDR systematic review; therefore, the review included three uncontrolled, manufacturer-sponsored studies conducted in patients with a diagnosis of aHUS, with or without identified gene mutations. Studies C08-002 (N = 17) and C08-003 (N = 20) were phase 2, prospective, multicentre, single-arm, open-label trials conducted in adults and adolescents ages 12 to 17 years. The study medication was administered for 26 weeks. Study C09-001 was a retrospective chart review of 30 patients that included children (0 to 11 years), adolescents (12 to 17 years), and adults. In study C08-002, patients were included if they were intolerant to PT or were resistant to PT, despite four or more treatments in the week before the start of study treatment. In study C08-003, patients were included if they were PT sensitive and had stable platelet counts during PT treatment. In study C09-001, both PT-resistant and PT-sensitive patients were considered for inclusion.

The trials included North American and European patients. The prospective trials were mainly conducted in adults (median 28 years) with more than 60% of patients being women; whereas, 50% of the patients in the retrospective chart review were children younger than 12 years, with an equal proportion of males and females. In studies C08-002 and C09-001, 40% of patients were experiencing their first attack of aHUS; whereas, in study C08-003, 25% of patients were experiencing a first attack. In studies C08-002 and C08-003, 35% and 10% of patients had received dialysis within the two months before eculizumab treatment respectively. In study C09-001, 37% of patients had at least gone through one dialysis session. Approximately 40% of patients had received a kidney transplant across all trials.

Outcomes

Outcomes were defined a priori in the CDR systematic review protocol. Of these, CDEC discussed the following:

- Mortality — a safety endpoint in the included studies.
- PT-free status — the number of PT sessions before and during eculizumab therapy.
- Dialysis-free status — the number of dialysis events before and during eculizumab therapy.
- Health-related quality of life (HRQoL) — measured with the European Quality of Life Scale (EuroQol-5D time trade off index and the visual analogue scale [VAS]).
- TMA event-free status — absence of the following three events: decrease in platelet count of > 25% from baseline; PT while patient is receiving study drug; and new dialysis.
- Complete TMA response — defined as hematologic normalization and 25% reduction from baseline in serum creatinine.
- Hematologic normalization — normalization of both platelet count and lactate dehydrogenase.
- Chronic kidney disease (CKD) stage — improvement by at least one CKD stage.
- Serious adverse events, adverse events, and withdrawals due to adverse events.

The primary end points were platelet count change (C08-002) and the proportion of patients who achieved TMA event-free status (C08-003). If statistically significant, then a second primary end point, the proportion of patients who achieved hematologic normalization, was evaluated.

Results

Efficacy

- There were no deaths in study C08-002 or C08-003 and two patients died in C09-001.
- All but one patient discontinued PT while on eculizumab treatment in the prospective trials (C08-002 and C08-003). In study C09-001, 30% of patients continued to receive PT while on eculizumab.
- In study C08-002, patients who had required dialysis pre-eculizumab (35%) were able to discontinue dialysis during eculizumab treatment, and one patient who was dialysis-free before eculizumab treatment required dialysis while on the study drug. In study C08-003, two patients who had received dialysis before eculizumab therapy were unable to discontinue dialysis during treatment with eculizumab. There were no new dialysis cases in study C08-003. In study C09-001, patients who had received dialysis were able to discontinue dialysis while on eculizumab treatment. There were two new dialysis patients during the treatment period of study C09-001.
- Patients' HRQoL was improved in both prospective trials; improvements were greatest in PT-resistant/intolerant patients (study C08-002). Some PT-sensitive patients (study C08-003) experienced deterioration in the HRQoL score while on eculizumab treatment.
- In studies C08-002, C08-003, and C09-001, 88%, 80%, and 57% of patients (respectively) were TMA event-free.
- In studies C08-002 and C08-003, 65% and 25% of patients (respectively) experienced a complete TMA response. TMA response was sustained for a mean of 120 days (standard deviation [SD] 49) in study C08-002 and for a mean of 80 days (SD 40) in study C08-003.
- In studies C08-002 and C08-003, 76% and 90% of patients (respectively) experienced a normalization of platelet count and lactate dehydrogenase level during the treatment period.
- In studies C08-002, C08-003, and C09-001, 59%, 35%, and 40% of patients (respectively) improved by at least one stage in CKD; 65%, 15% and 40% of patients (respectively) had a

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decrease of $\geq 25\%$ in serum creatinine level; and 47%, 5% and 37% of patients (respectively) improved by ≥ 15 mL/minute/1.73 m² in estimated glomerular filtration rate (eGFR).

Harms (Safety and Tolerability)

- Almost every patient in the prospective trials experienced at least one adverse event (97%); whereas, in the retrospective chart review, 73% of patients reported having at least one adverse event.
- The most common adverse events were hypertension (47%), headache (41%), and anemia (35%) in study C08-002; upper respiratory tract infection (40%) and hypertension (25%) in C08-003; and pyrexia (30%) and cough (23%) in C09-001. In all three trials, patients experienced diarrhea (27% to 35%) and vomiting (15% to 29%).
- Fifteen patients (88%) and five patients (25%) reported at least one serious adverse event in studies C08-002 and C08-003 respectively.
- In studies C08-002 and C08-003, there were 38 episodes of infection. Five infections were considered serious, for which patients required hospitalization.
- A total of 35% of patients experienced at least one hypertension-related event including six serious adverse events.
- One patient experienced gastrointestinal bleeding that was deemed to be possibly related to eculizumab treatment (study C08-003).
- One patient withdrew from study C08-002 due to an adverse event.

Cost and Cost-Effectiveness

The manufacturer submitted an economic analysis comparing eculizumab plus non-biologic supportive care (excluding plasma exchange) with non-biologic supportive care (including plasma exchange) over a one-year time horizon, where supportive care included dialysis and supportive care treatment for end-stage renal disease, hospitalization, and physician consults. Due to a dearth of information available for the management of patients with aHUS, the manufacturer consulted five Canadian experts with an interest in aHUS to identify all relevant health care resources for the management of patients with aHUS, and the expected frequency of use. The manufacturer reported the annual cost per patient of treatment with eculizumab plus non-biologic supportive care (excluding plasma exchange) to be \$746,899 in the first year, compared with a cost of \$210,056 for treatment with plasma exchange plus non-biologic supportive care.

A number of limitations were noted with the economic submission:

- Quality of life information was collected in the eculizumab clinical trial, which could have been used to present a more informative cost-utility analysis to examine the relative cost-effectiveness of eculizumab in patients with aHUS.
- The difficulty in diagnosing aHUS in patients may substantially inflate the total cost of treatment (budget impact) for public plans due to the extremely high price of eculizumab.
- The eculizumab product monograph indicates that treatment should not be stopped once initiated. Thus, the cost of eculizumab treatment would be incurred for the remainder of the patient's life, the length of which is unknown as there is no reliable data indicating the life expectancy of a patient with aHUS, before or after treatment with eculizumab.

- The estimates of cost and duration of plasma exchange, which drive non-biologic supportive care, are highly uncertain; this then has an impact on the determination of the assessment of incremental cost for eculizumab.
- No information was presented to assess the efficacy of the PT.
- Eculizumab may be used in combination with plasma exchange, which was not accounted for in the manufacturer's economic submission. The CDR re-analysis showed that concomitant treatment would greatly increase the incremental cost of treatment of eculizumab up to \$940,084 per patient per year.

The annual drug cost per patient for eculizumab treatment ranges from \$121,356 to \$728,136, depending on the weight of the patient. The annual incremental cost of eculizumab treatment may lie between \$500,000 and \$600,000 per patient compared with non-biologic supportive care plus plasma exchange; however due to the paucity of data, there is considerable uncertainty with this estimate.

Other Discussion Points:

CDEC noted the following:

- Eculizumab was evaluated in a broad selection of patients with aHUS, including both PT-resistant and PT-sensitive patients, patients with first and subsequent episodes of aHUS, those with and without genetic mutations, patients with or without kidney transplants, and patients with and without a history of dialysis. Despite subgroup analyses conducted for the prospective trials, the small number of patients included prevented the identification of subpopulations that are most likely to benefit from eculizumab therapy.
- Given that the studies included in the CDR review were uncontrolled and of short duration, the impact of eculizumab on the development of renal complications and mortality is unclear.
- Baseline EQ-5D scores were higher than might be expected for a severe disease, including 11 patients who reported a score of 0.94, which could make assessing improvements difficult due to a ceiling effect.
- The included studies mainly enrolled adults and a few adolescents; therefore, a formal evaluation in pediatric patients would be beneficial.
- There are limited data for use of eculizumab in children (< 12 years) with aHUS.
- Limitations of currently available diagnostics have the potential to result in their use where there is suspicion but not confirmation of aHUS, with significant cost consequence.

Research Gaps:

CDEC noted that there is insufficient evidence regarding the following:

- Efficacy and safety of eculizumab in children (< 12 years) with aHUS.
- Clinical benefit of eculizumab on overall survival for patients with aHUS.
- Clinical indicators of therapeutic failure for patients treated with eculizumab.
- Effect of eculizumab on hemoglobin levels in the absence of treatment with erythropoietin.
- Relative benefit of eculizumab in relation to PT.
- Subgroups likely to respond or need ongoing therapy.

CDEC Members:

Dr. Robert Peterson (Chair), Dr. Lindsay Nicolle (Vice-Chair), Dr. Ahmed Bayoumi, Dr. Bruce Carleton, Ms. Cate Dobhran, Mr. Frank Gavin, Dr. John Hawboldt, Dr. Peter Jamieson, Dr. Julia Lowe, Dr. Kerry Mansell, Dr. Irvin Mayers, Dr. Yvonne Shevchuk, Dr. James Silvius, and Dr. Adil Virani.

June 19, 2013 Meeting**Regrets:**

None

Conflicts of Interest:

None

About This Document:

CDEC provides formulary listing recommendations or advice to CDR participating drug plans. CDR clinical and pharmacoeconomic reviews are based on published and unpublished information available up to the time that CDEC deliberated on a review and made a recommendation or issued a record of advice. Patient information submitted by Canadian patient groups is included in the CDR reviews and used in the CDEC deliberations.

The manufacturer has reviewed this document and has not requested the removal of confidential information in conformity with the *CDR Confidentiality Guidelines*.

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